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Medicinal plants and secondary metabolites for diabetes mellitus control

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ABSTRACT

Diabetes mellitus is one of the most common and complex problems of modern societies which has caused many economic and social problems. Because diabetes has no definite treatment, the use of traditional medicine seems to be an appropriate solution to control and manage it. Studies revealed that *Vaccinium Arctostaphylos* L., *Securigera securidaca* L., *Gymnema sylvestre* L., *Atriplex halimus* L., *Camellia sinensis* L., *Ginkgo biloba* L., *Mamordica charantia* L., *Citrullus colocynthis* (L.) Schrad., *Allium cepa* L., *Allium sativum* L., *Silybum marianum* (L.), Gaertn and *Trigonella foenum graecum* L. are effective against diabetes. Flavonoids, quercin, metformin, quinolizidine, anthocyanin, catechin and flavone, phenylpropanoids, lipoic acid and coumarin metabolites were introduced major impact on diabetes. With regard to the study of plants and their metabolites and the mechanisms of their influence, it is clear that these plants have the potential to reduce blood sugar and diabetes and be considered as candidates for preparing new drugs. Combination of plants extracts or their components may also have synergistic effects to better act on diabetes.

1. Introduction

Diabetes mellitus is one of the most common and complex problems of modern societies which has caused many economic and social problems. Type I diabetes results from defects in insulin secretion, while the pathogenesis of type II diabetes is associated with a course of progressive insulin resistance in liver and peripheral tissues, reduced β-cell mass and/or impaired insulin secretion[1,2]. Diabetes mellitus causes changes in metabolism of carbohydrates, fats and proteins which result in hyperglycemia, glycosuria, hyperlipidemia and also atherosclerosis[3-5]. Hyperglycemia due to diabetes is associated with long-term damage, destruction and failure of function of various organs[6,7]. One of these organs is the liver and a range of disorders from fatty change to liver cirrhosis and cancer can occur[8]. Liver is a non-insulin dependent organ and has an important role in lipid and glucose homeostasis[9]. In addition, studies showed tissue damages caused by diabetes can be attributed to oxidative stress[10-13]. Vascular complications of diabetes, including retinopathy, neuropathy, nephropathy and macrovascular disorders are considered as the major causes of mortality in diabetic patients[14-17].

Long-term increase of glucose in diabetes is thought to be the main cause of some disorders like microangiopathy, macroangiopathy, poor antioxidant defense system and impaired lipid metabolism. These disorders can cause short-term and long-term effects which can cause physiological damage to various organs of the body[18,19]. Delayed complications of diabetes such as nephropathy, retinopathy, cardiovascular complications, neuropathy, skin ulcers, high blood pressure and weight gain are more common and more researches have been done about them[20,21]. The number of diabetic patients referred to physicians is increasing significantly. Diabetes affects more than 140 million people in the West countries and the number will reach 300 million by 2025[22].

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Synthetic drugs are used to treat or prevent diabetes, but they have side effects[23]. Due to this issue and their high costs, nowadays interests in finding effective natural ingredients has increased. In recent decades, many studies have been done on the therapeutic properties of herbs and these elements have been proposed for the treatment of various hard curable diseases such as athrosclerosis[12,24], cardiovascular diseases[25,26], neurological disorders[27,28] and cancer[29,30]. These conditions involve many changes, including alterations in redox state[31,32], and medicinal plants with antioxidant activity have the ability to counteract these situations and always been considered as a healthy source of health promotion[11,33].

Before the discovery of anti-diabetic drugs and insulin, diabetic patients used medicinal plants and traditional medicine[34]. Plants may operate through different mechanisms that effect on blood sugar. Some of them may have insulin kinase[35], and some other may inhibit insulinase activity[36], and others may increase reconstruction of pancreatic β cells[37]. Fibers of plants may also interfere with the absorption of carbohydrates and thus have an effect on blood glucose[38].

There are known herbs and secondary metabolites that are effective in diabetes management and control. In this paper the most effective herbs and plant metabolites for diabetes mellitus will be discussed.

2. Medicinal plants and metabolites on diabetes

2.1. The most effective herbs for diabetes

2.1.1. Vaccinium arctostaphylos L.

In traditional medicine this plant is used for treatment of diabetes. This herb contains anthocyanoside myrtillin which has similar mechanism with insulin[39].

2.1.2. Securigera securidaca L.

Securigera securidaca L. has significant effect on blood glucose levels in a mouse model of diabetes. It is a native plant of Iran and has a different mechanism from effect of glibenclamide[40].

2.1.3. Gymnema sylvestre L. (G. sylvestre)

This herb is effective on both types of diabetes by inhibition of absorption of glucose in the digestive tract resulting in glucose excreted and also by reconstruction of damaged beta cells[41,42].

2.1.4. Atriplex halimus L.

In animal models it can exerts a significant effect on blood sugar. This herb contains fiber, protein and trace elements such as chromium. Studies showed that administration of three grams of dried leaves of the plant reduces blood sugar in type II diabetics[38].

2.1.5. Camellia sinensis L.

Green tea contains flavanols like catechin, epicatechin, epigallocatechin and gallocatechin. These compounds are antioxidants. Powdered green tea increases insulin resistance. Also, polyphenols in this herb have antioxidant mechanism and have antidiabetic properties[43-45].

2.1.6. Ginkgo biloba L.

This herb contains flavoglycosides. It has effect on complications of diabetes and increases the blood flow and indirectly can be effective on diabetic wound healing because of increased blood circulation[46].

2.1.7. Mamordica charantia L.

Raw fruit, dried extract, and its juice aer effective on diabetes. This herb contains polypeptide which is similar in structure to insulin and reduces blood sugar levels in diabetics Type I[47].

2.1.8. Citrullus colocynthis (L.) Schrad.

According to the traditional botanical knowledge as well as clinical studies, *Citrullus colocynthis* fruit has anti-diabetic effects[48].

2.1.9. Allium cepa L.

Allyl propyl disulfide is a sulfur compound in onions that have glucose lowering effects[49].

2.1.10. Allium sativum L.

Allyl disulfide oxide as the active ingredient in garlic has a blood sugar lowering effects[38].

2.1.11. Silybum marianum (L.) Gaertn

Silybin and silydianin which are flavonoids in this herb, can increase cellular uptake of glucose[50].

2.1.12. Trigonella foenum graecum L.

The seeds of this herb contain bioactive substances such as trigonelline, coumarin and nicotinic acid. Seeds have antidiabetic properties. Fifteen grams of soaked powdered seeds can reduce blood glucose in type II diabetic patients. Amino acids and fiber, have been introduced as antidiabetic agents[51].

2.2. The most common metabolites influencing diabetes

Although there is a wide list of natural anti-diabetes drugs, however, citing all natural antidiabetic plants and their components is out of the scope of this paper. We tried to summarize the most biologically active secondary metabolites with anti-diabetes activity in Table 1 discussing some of them bellow[52].

2.2.1. Flavonoids

Flavonoids are constituents of fruits, vegetables and herbs. Flavonoids (quercetin) can stimulate insulin secretion. Quercetin inhibites aldolase reductase in diabetic patients. Quercetin exists in cabbage, green tea, apple, onion, beans and nuts, and such herbs like *Ginkgo biloba*[53].

Metformin or dimethyl-biguanide is an oral anti-diabetic herbal ingredient which is derived from plant *Galega officianalis*. It has a wide variety of other therapeutic effects[21,54].

Table 1

The most biologically active secondary metabolites with anti-diabetes activity.

Natural compounds class	Name	Mechanism of action and uses
Alkaloids	Casuarine 6-O-α-glucoside	α-Glucosidase inhibitor
	Isoquinoline alkaloids: schulzeines A, B and C	α-Glucosidase inhibitor
	Tecomine, 5β-hydroxyskitanthine, boschniakine	Stimulate basal glucose uptake rate in rat adipocytes
	Two new pyrrolidine alkaloids : radicamines A and B	α-Glucosidase inhibitor
	Three quinolizidine alkaloids: javaberine A, javaberine A hexaacetate and javaberine B hexaacetate	Inhibitors of TNF-α production by macrophages and fat cells. Dietary supplement for prevention of diabetes
	Three quinolizidine alkaloids: lupanine, 13-α-hydroxylupanine, 17-oxo-lupanine	Glucose-induced insulin release enhancement from isolated rat islet cells which was dependent on the glucose concentration
	Five isoquinoline: alkaloids berberine, chloride berberine, sulfate berberine, iodide, palmatine sulfate, palmatine chloride	Aldose reductase inhibitor
Flavonoids	6-Hydroxyapigenin, 6-hydroxyapigenin-7-O-β-D-glucopyranoside, 6-hydroxyluteolin- 7-O-β-D-glucopyranoside, 6-hydroxyapigenin-7- O-(6-O-feruloyl)-β -D-glucopyranoside, 6-hydroxyluteolin-7-O-(6-O-feruloyl)-β-D-glucopyranoside	α-Glucosidase inhibitor
	Myrciacitrin I, II, III, IV and V	Aldose reductase inhibitory activity.
	Quercetin 3-O-α-L-arabinopyranosyl-(1$\rightarrow$2)-β-D-glucopyranoside, Kaempferol 3-O-β-D-glucopyranoside (astragalin), quercetin 3-O-β-D-glucopyranoside (isoquercitrin)	Glycation inhibitors
Terpenes	Lactucain A, B and C	Moderate lowering of plasma glucose
	3,22-Dihydroxyolean-12-en-29-oic acid, tingenone, tingenine B, regeol A, triptocalline A, mangiferin	Aldose reductase inhibitory activity
	Centellasaponin A	Aldose reductase inhibitory activity
	Abietane-type diterpenoids: danshenols A and B, dihydrotanshinone I, tanshinone I, cryptotanshinone, tanshinone IIA (-)-danshexinkun A	Aldose reductase inhibitory activity
	Triterpenedehydrotrametenolic acid	Insulin sensitizer
	Corosolic acid (GlucosolTM)	Glucose transport-stimulating activity
Phenolics	7′-(3′,4′-Dihydroxyphenyl)-N-[(4 methoxyphenyl)ethyl] propenamide, 7′-(4′-hydroxy-3′methoxyphenyl)-N-[(4butylphenyl)ethyl] propenamide	α-Glucosidase inhibitor
	(7S,8S)-syringoylglycerol 9-O-β-D-glucopyranoside (7S,8S)-Syringoylglycerol-9-O-(6′- O-cinnamoyl)-β-D- glucopyranoside	α-Glucosidase inhibitor
	Tetra- and penta-O-galloyl-β-D-glucose	Potent aldose reductase inhibitory activities.

2.2.2. Quinolizidine alkaloids

Some alkaloids, such as sparteine and lupanine are derived from quinolizidine which is a heterocyclic compound and contains nitrogen. About 150 alkaloids of quinolizidine group are known in various species of *Lupinus*. These compounds can stimulate insulin secretion in a glucose-dependent manner and partly through inhibition of adenosine triphosphate dependent potassium channels in the beta cells of the pancreas[55].

Metformin reduces blood glucose and may eliminate insulin sensitivity, but in the absence of insulin (as in type I diabetes) it is ineffective. Mechanism of metformin in non-insulin dependent diabetic patients is attributed to reducing the output of hepatic glucose and increasing peripheral glucose uptake[56].

Flavonoids are found in many plants: anthocyanins (petunidin in raspberry, peonidin in strawberry, pelargonidin in tea, delphinidin in red grapes, cyanidin in cherry and malvidin in red wine), catechin (epicatechin in red wine and catechin in tea), flavone (quercetin in potato skins, apigenin in olive, luteolin in parsley, sibelin the celery, myricetin in broccoli and rutin in lettuce), flavanone (taxifolin, naringenin, naringin, fisetin and hesperetin in peel and fruit of citrus)[57].

Phenylpropanoids, a class of organic compounds derived from phenylalanine are a diverse group of plant secondary metabolites. They include flavonoids, stilbenoids and lignins. Different compounds in this group have hypoglycaemic properties[58].

Lipoic acid exists in green vegetables such as broccoli, spinach and animal products of ruminants such as the heart, liver, kidney and skeletal muscles. Clinical studies have shown that the lipoic acid improves glucose metabolism in type II diabetic patients by stimulating the uptake of glucose by the rapid transfer through glucose channels (glucose transporter type 4) from intracytosol vesicles to plasma membrane[59-61].

Coumarin is the major compound of turmeric which is also effective on diabetes mellitus induced by streptozotocin and nicotine amide. The mechanism is via increased hexokinase activity and glucose-6-phosphate dehydrogenase, namely increase in glucose decomposition and the significant reduction in titer of enzymes glucose 6-phosphatase and fructose-1, 6-biss phosphatase (decrease gluconeogenesis)[62].

3. Conclusions

Nowadays, the data on medicinal plants and their biological activities are tremendously increasing[34,63,64]. However, it is impractical to specify the performance of a mixture which present in the plant extracts comprising a wide range of phytochemical constituents, to only a single compound from that extract[65]. Metabolites might act as lead compounds for the discovery of different new classes of possibly potent and safe anti-diabetic agents. However, attention should be given for the identification of the typical modes of action of their extracts and the isolated pure compounds[66].

Many classes of secondary metabolites of herbal medicines, such as alkaloids, phenolics, flavonoids, terpenoids and others have been shown promising anti-diabetic activities. These constituents may be considered as a promising source of hypoglycemic agents with minimal side effects.

Finding the promising candidates for the treatment of diabetes mellitus could be achieved through evaluation of the anti-diabetic properties of different medicinal plant extracts, their fractions and isolated components, followed by preliminary phytochemical screening, and their toxicities[23,67]. Although various compounds with different mechanism of actions have been shown to reduce blood glucose, however, antioxidant activity of these plants has a crucial role in their anti-diabetes actions[10,11,13,32,33,68].

Oxidative stress has been implicated not only in diabetes mellitus, but also in a wide variety of pathological conditions such as cancer[69,70], neurological disorders[71,72], ischemia/reperfusion[73,74]. These conditions involve many changes, including impaired glucose tolerance, alterations in the thiol/disulphide redox state, and activation of inflammatory processes[11,75,76]. They are also associated with increased activity of nicotinamide adenine dinucleotide phosphate oxidase or induction of xanthine oxidase with subsequent increase in oxidative stress during chronic inflammation and the generation of damage, particularly during diabetes and ischemia/reperfusion. Exposure to agents that increase the oxidative stress might accelerate the initiation of pathological changes such as diabetes. Therefore, antioxidant activity evaluation of the plants will give a preliminary prediction for their anti-diabetic activities[77,78].

Pharmacological evaluation to recognize the most active candidates will be determined through measuring different biochemical parameters such as serum glucose, insulin, glycosylated hemoglobin, lipid profile, serum urea and creatinine, plasma aspartate transaminase and alanine transaminase. The anti-diabetic properties will also be further confirmed through microscopical examinations of the pancreatic sections[4,16,18].

Botany traditional knowledge and clinical knowledge are linked together. A lot of clinical trials have taken knowledge of botany source. Many of the traditional knowledge of medicinal plants have been routinely taken in the treatment of various diseases from this knowledge[79-87]. Therefore, the use of more traditional resources have been recently recommended until further herbs in the treatment of diabetes presented, and with clinical research production of new herbal drugs were developed.

Medicinal plants are still considered as a promising source for drug discovery and are playing a pivotal role in drug development programs. Moreover, many medicinal plants provide a rich mine for bioactive chemicals that are mostly free from undesirable adverse effects and of powerful pharmacological actions.

Much effort should be afforded to optimize a procedure for antidiabetic screening of different plants' extracts as well as isolating bioactive compounds for the discovery of new natural herbal antidiabetic drugs that can be used as alternatives to synthetic oral hypoglycemic drugs with less or even no prominent side effects.

Conflict of interest statement

We declare that we have no conflict of interest.

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